Important Advances in Clinical Medicine

Epitomes of Progress—Anesthesiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in anesthesiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in anesthesiology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Anesthesiology of the California Medical Association and the summaries were prepared under its direction.

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Dantrolene: Specific Drug Therapy for Malignant Hyperthermia

MALIGNANT HYPERTHERMIA is a fulminant hypermetabolic crisis induced by anesthetic trigger agents in genetically susceptible persons. The full-blown syndrome, with tachycardia, cardiac dysrhythmias, unstable blood pressure, fever, rigidity, hypoxemia, lactic acidosis, hyperkalemia and myoglobinemia, has a mortality of 60 percent. This syndrome has been reported in patients ranging in age from 3 months to 70 years.

Malignant hyperthermia results from a defect of membrane calcium transfer in skeletal muscle. The sarcoplasmic reticulum, in response to a triggering stimulus, releases an abnormally large amount of calcium because of abnormal "leakiness," or by its inability to reaccumulate calcium from the myoplasm back into intracellular storage sites. Excess myoplasmic calcium produces an abnormal amplification of excitation-contraction coupling. The resulting hypermetabolism and continued contraction of skeletal muscle generate heat, exhaust adenosine triphosphate stores, uncouple mitochondrial oxidative phosphorylation, and lead to further cellular and membrane derangements.

Until recently the treatment of malignant hyperthermia consisted only of supportive measures —discontinuance of anesthesia, hyperventilation with 100 percent oxygen, sodium bicarbonate for metabolic acidosis, procainamide for cardiac dysrhythmias, cooling, diuretics to prevent myoglobin from precipitating in the renal tubules, and treatment of hyperkalemia. Although it may restore blood gas and other laboratory values, supportive therapy does not alter the underlying and continuing pathological defect.

Dantrolene sodium, which acts to prevent excessive release of intracellular calcium, is one of several hydantoins synthesized by Snyder and associates in 1967 that proved to have muscle relaxant properties. Extensively investigated, dantrolene is known to act directly on skeletal muscle but has no effect on smooth and cardiac muscle. It does not affect neuromuscular transmission or electrically excitable surface cell membranes. Van Winkle showed that dantrolene is pharmacologically active within the sarcotubular system where it suppresses the release of calcium. It has proved effective in the treatment and reversal of malignant hyperthermia in both swine and humans.

Dantrolene is not a substitute for aggressive, supportive therapy—it is a specific adjunct to

established treatment. It is supplied as a lyophilized powder which is dissolved in sterile water. The initial intravenous dose for children and adults is 1 mg per kg of body weight, repeated as necessary for persistent physiological and metabolic abnormalities up to a cumulative dose of 10 mg per kg of body weight. The average cumulative intravenous dose required to abort the clinical manifestations in humans is 2.5 mg per kg of body weight. Dantrolene given orally in doses of 1 to 2 mg per kg of body weight four times a day for one to three preoperatively may be prophylactic in known malignant hyperthermia reactors. There are no reported side effects with short-term dantrolene therapy.

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Hazards of Discontinuing Drugs Before Anesthesia

RESERPINE THERAPY for hypertension used to be discontinued before elective operations. Now it is felt that there is less anesthetic risk to hypertensive patients if this medication is continued up to the time of the surgical procedure. In fact, some danger of excessive cardiovascular stress arises if, inadvertently, antihypertensive therapy is not continued. On the other hand, the *Physician's Desk Reference* suggests that drugs such as monoamine oxidase inhibitors, tricyclic antidepressants and propranolol should be discontinued preoperatively. Because discontinuation of these drugs is not without hazard (such as depression, suicide, angina or myocardial infarction), the benefits and risks must be carefully weighed.

Few patients receive monoamine oxidase inhibitors. Their interaction with indirect-acting amines is widely recognized and generally avoidable. Further, their interaction with meperidine, resulting in coma, hyperpyrexia and hypertension, although not understood, is also avoidable. However, only a minority of anesthetists view continuing a regimen of monoamine oxidase inhibitors as desirable because the adverse effects are difficult to manage.

Unlike the monoamine oxidase inhibitors, the tricyclic antidepressants do not appear to cause severe adverse effects. While they potentiate the cardiovascular effects of exogenous catecholamines, this interaction can be avoided or controlled. Tachyarrhythmia has been reported following the simultaneous administration of the neuromuscular blocking agent pancuronium (Pavulon) in combination with the inhalation anesthetic agent halothane (Fluothane) to patients receiving long-term imipramine (Imavate, Presamine or Tofranil) therapy. Because this combination of drugs usually can be avoided, tricyclic antidepressants in therapeutic doses can be safely continued perioperatively. However, it should be noted that continuation of tricyclic antidepressants restricts the choice of anesthetic agents.

An initial series of case reports on patients undergoing cardiac operations seemed to support the view that propranolol (Inderal) interacted adversely with inhalation anesthetic drugs to produce severe myocardial depression and impaired ability to respond to cardiovascular stresses such as hemorrhage. However, reports of rebound phenomena after withdrawal of propranolol soon appeared. In hypertensive patients, abrupt withdrawal of propranolol was followed by 2 to 15 days of hypersensitivity to catecholamines. However, the course of hypersensitivity is such that it permits operations to be done within 48 hours of withdrawal. In patients with severe coronary disease and angina, exacerbation of coronary insufficiency symptoms and even acute myocardial infarction and death have been reported. This "rebound" may be the result of continued physical activity or emotional stress on a heart that is no longer protected by the beta-adrenergic blocking drug. In a large controlled study of coronary artery bypass graft patients, those who continued to receive propranolol up to the day of the operation did as well as the patients in whom propranolol therapy was discontinued. It should be noted that these study patients had intensive cardiovascular monitoring and specialists in cardiac anesthesia overseeing their anesthetic care. Nevertheless, if a surgical patient does not have the signs of excessive beta receptor blockade (bradycardia), continuation of propranolol administration does not appear to present unusual difficulties.

Antihypertensive agents should be given up to the time of operation. Clonidine (Catapres), however, presents a special problem because it has a